

CLAIMS

Pharmaceutical Composition

1. A prodrug comprising a drug moiety bound to a carrier framework, the prodrug being activated by aromatic oxidation of the carrier framework to release the drug moiety.

2. A prodrug according to claim 1, being activated by aromatic hydroxylation.

3. A prodrug according to claim 2, being activated by enzymatic aromatic hydroxylation.

4. A prodrug according to any one of the preceding claims, being an anti-tumour prodrug.

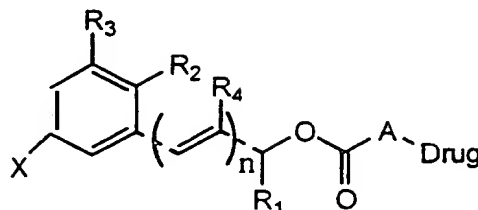
5. A prodrug according to any one of the preceding claims, the drug moiety being a cytotoxic or cytostatic agent.

6. A prodrug according to claim 5, a cytotoxic drug moiety being selected from any one of the group of colchicine, esperimycin, taxol, daunomycin, staurosporin, nitrogen mustard, and 5-fluorouracil.

7. A prodrug according to any one of the preceding claims, being activated by hydroxylation by CYP1B1.

8. ~~A prodrug according to any one of the preceding claims, the drug moiety being an antimetabolic agent, an alkylating agent, an antifolate, an antimetabolite, a DNA-damaging agent or an enzyme-inhibitor.~~

9. A prodrug according to any one of the preceding claims, having the formula (Z):



wherein:

$\text{X} = \text{H}, \text{OH}, \text{OMe}$ or $\text{N}(\text{CH}_3)_2$; and

$n = 0-6$;

and:

$\text{R}_1 = \text{H}, \text{C}_{1-4}$ lower alkyl, or together with R_2 forms part of a cycloalkyl group which may be further substituted to form part of a polycyclic cycloalkyl group, or with R_2 forms part of a steroidal carbon framework;

$\text{R}_2 = \text{H}, \text{OMe}, \text{C}_{1-4}$ lower alkyl, or together with R_1 and/or R_3 forms part of a cycloalkyl, polycyclic cycloalkyl or steroidal carbon framework, or forms part of a polycyclic aromatic group by linkage to R_4 ;

$\text{R}_3 = \text{H}, \text{OMe}, \text{C}_{1-4}$ lower alkyl or together with R_2 forms part of a cycloalkyl, polycyclic cycloalkyl or steroidal carbon framework; and

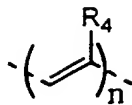
$\text{R}_4 = \text{H}$ or is fused directly to the aromatic position designated by R_2

and either:

the drug moiety is derived from a drug having a free amino, hydroxyl or thiol group and which links it to the rest of the prodrug, such that A represents NH, NR ($\text{R} = \text{C}_{1-4}$ lower alkyl), O or S; or

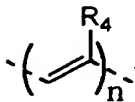
the drug moiety is derived from a drug having a carboxylate group, an ester linkage joining it to the rest of the prodrug and A being absent

10. A prodrug according to claim 9, the olefin linkage



having a cis- or trans-geometry.

11. A prodrug according to claim 9, the olefin linkage



being acyclic or cyclic.

12. A prodrug according to claim 9, the olefin linkage



forming part of an aromatic or polycyclic aromatic system.

13. A prodrug according to any one of the preceding claims, the linkage to the drug moiety from the carrier framework being from a hydroxyalkyl group in the prodrug via a carbamate, carbonate or thiocarbonate linker to an amino, hydroxy or thiol group in the drug moiety.

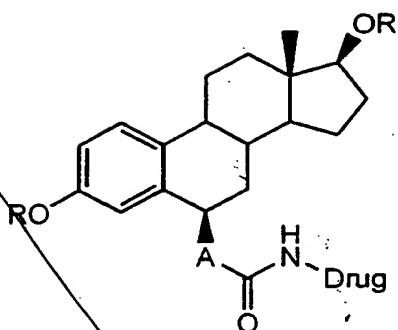
14. A prodrug according to any one of the preceding claims, having a steroid carbon carrier framework.

15. A prodrug according to claim 14, being derived from estradiol.

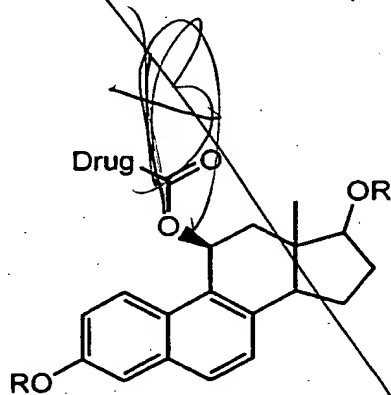
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16. A prodrug according to claim 15, having the formula of any one of formulae (I) - (IX):

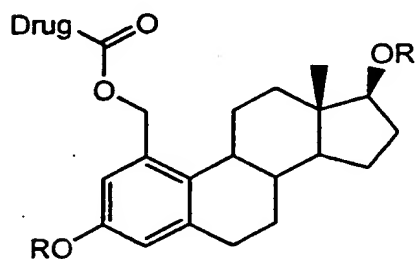
(I):



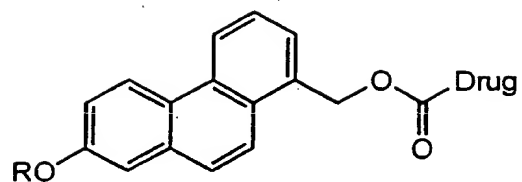
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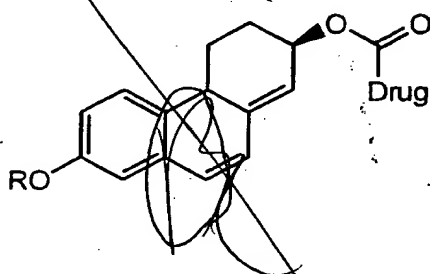
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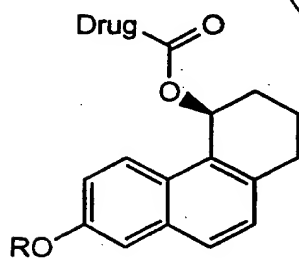
(IV):



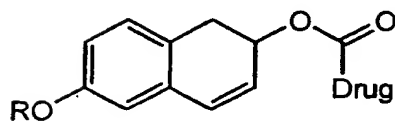
(V):



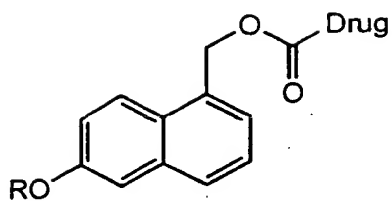
(VI):



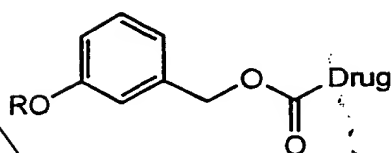
(VII):



(VIII):



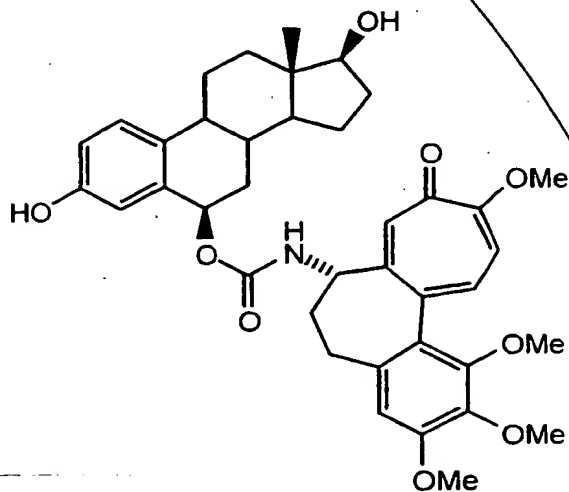
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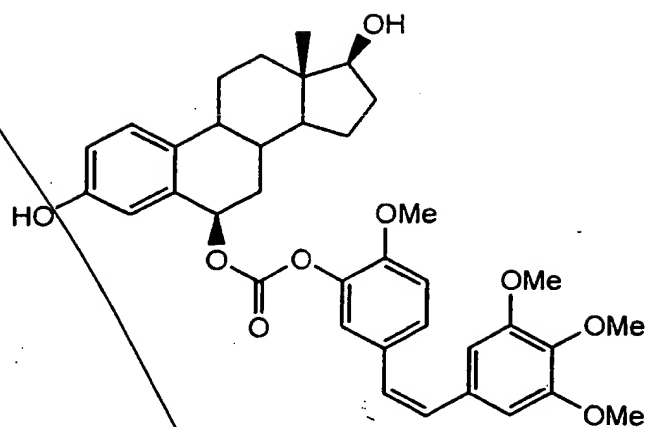
wherein -OR = -OMe or -OH

17. A prodrug according to claim 15, having the formula of any one of Formulae (X) - (XIII):

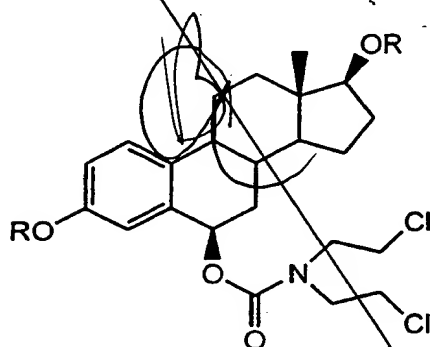
(X):



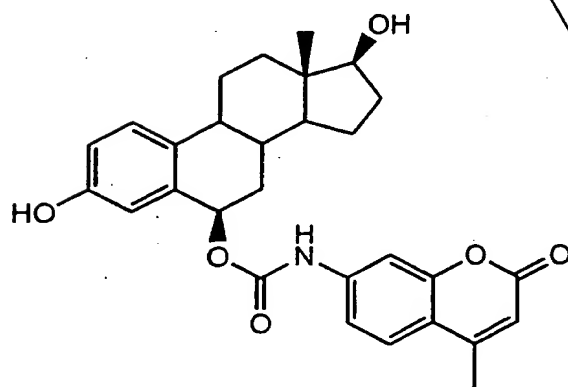
(XI):



(XII):



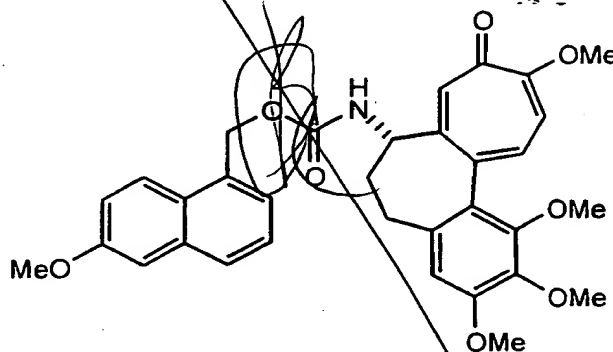
(XIII):



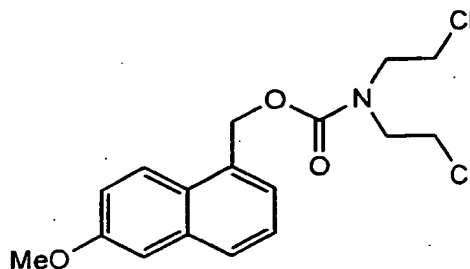
where R = H (Formula XIIa) or R=Me (Formula XIIb)

18. A prodrug according to any one of claims 1-13. having a polycyclic aromatic carrier framework.
19. A prodrug according to claim 18, being based on either one of the group of a naphthyl and phenanthryl structures.
20. A prodrug according to claim 19, having the formula of any one of formulae (XIV) - (XVII):

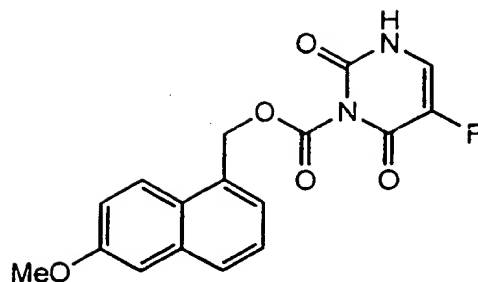
(XIV):



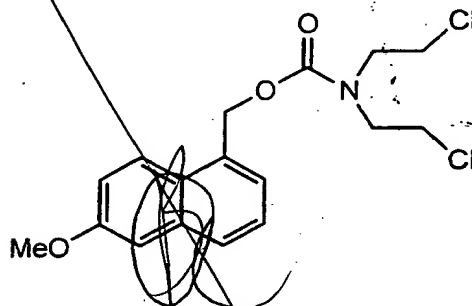
(XV):



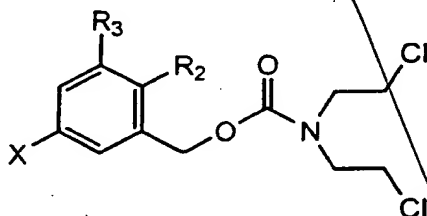
(XVI):



(XVII):



21. A prodrug according to any one of claims 1-13, having a substituted benzyl carrier framework.
22. A prodrug according to claim 21, having the general formula (Y):

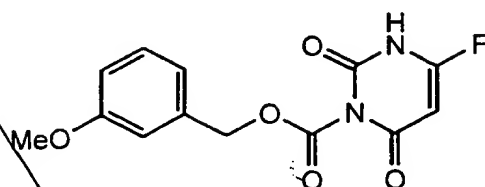


R_2 , R_3 and X being selected from any one of the group of:

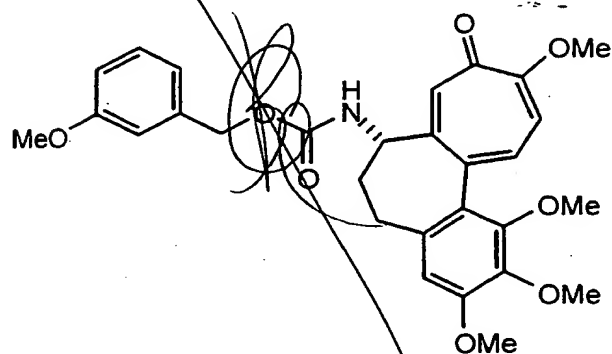
- $R_2 = H$, $R_3 = H$, $X = OMe$ (Formula XVIII);
- $R_2 = H$, $R_3 = OMe$, $X = OMe$ (Formula XIX);
- $R_2 = H$, $R_3 = H$, $X = H$ (Formula XX);
- $R_2 = OMe$, $R_3 = H$, $X = H$ (Formula XXI); and
- $R_2 = OMe$, $R_3 = H$, $X = OMe$ (Formula XXII).

23. A prodrug according to claim 21, having the formula of any one of formulae (XXIII) - (XXVIII):

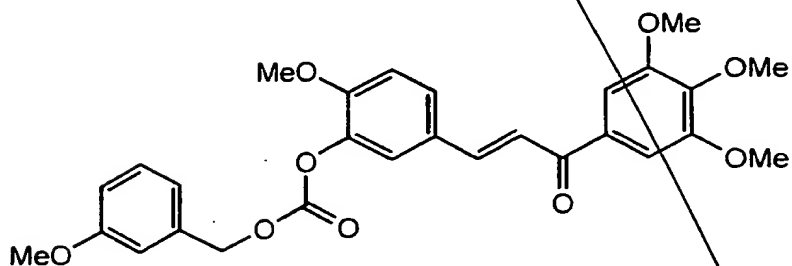
(XXIII):



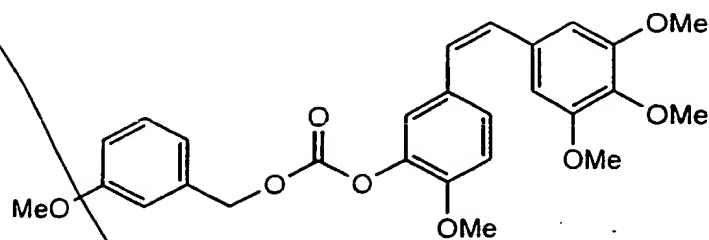
(XXIV):



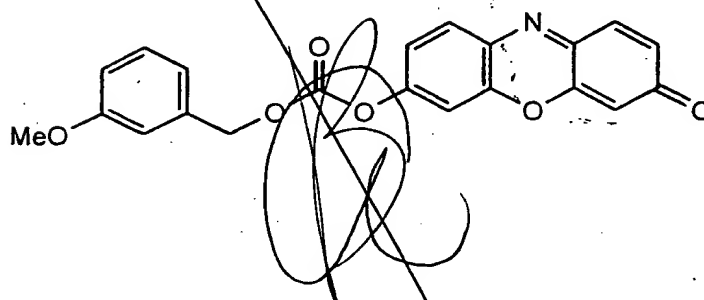
(XXV):



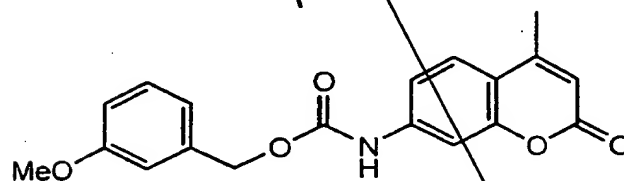
(XXVI):



(XXVII):



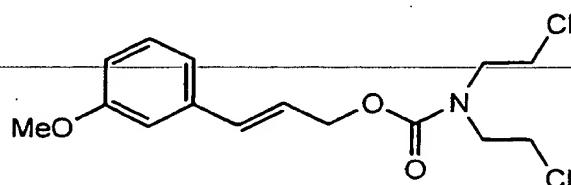
(XXVIII):



24. A prodrug according to any one of claims 1-13, having a cinnamyl carrier framework.

25. A prodrug according to claim 24, having the formula of any one of formulae (XXX) - (XXXII):

(XXX):



O=C1C=CC2=C(C=C1)OC3=CC=C(OC(=O)OCC=Cc4ccccc4)C=C3N2Cc1c(=O)oc2cc(ccc2c1)NC(=O)OCC=Cc3ccccc3

26. A prodrug according to any one of the preceding claims, its aromatic oxidation being by hydroxylation and causing the release of the drug moiety and carbon dioxide.
27. A prodrug according to any one of the preceding claims, for use in a method of treatment or diagnosis of the human or animal body.
28. The use of a prodrug according to any one of the claims 1-26 in the manufacture of a medicament for the treatment of a tumour.
29. A method of manufacture of a medicament for the treatment of a tumour, comprising the use of a prodrug according to any one of claims 1-26.
30. A method of treatment of a patient, comprising administering to the patient a prodrug according to any one of claims 1-26

31. A method of treatment according to claim 30, being a method of treatment of a tumour.
32. A method of detection of aromatic oxidation, comprising the steps of:
- I) contacting a sample with a prodrug according to any one of claims 1-26;
 - ii) detecting any product of aromatic oxidation of the prodrug; and
 - iii) correlating detection of the product of aromatic oxidation of the prodrug with aromatic oxidation activity.
33. A method according to claim 32, the aromatic oxidation activity being enzymatic.
34. A method according to claim 33, the aromatic oxidation activity being CYP1B1 aromatic oxidation activity.
35. A method according to any one of claims 32-34, being a method of detection of tumour cells.
36. A method according to any one of claims 32-35, being a method of diagnosis of the human or animal body.

add
C1

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V6

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